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Review of the major findings about Duane retraction syndrome (DRS) leading to an updated form of classification

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ABSTRACT

In view of all the reported evidence by electromyography in the 1970s, by histology in the 1980s, and by cerebral imagery since the 2000s, Duane retraction syndrome (DRS) has been described as the consequence of a congenital anomaly of the 6th cranial nerve nuclei with aberrant innervations by supply from the 3rd cranial nerve. Both genetic and environmental factors are likely to play a role when the cranial nerves and ocular muscles are developing between the 4th and the 8th week of gestation. New data from eye movement recordings contributed to better understanding the binocular control of saccades. Modeling of saccades in DRS seems promising for the quantification of the innervational deficit and the mechanical properties of the eye plant. The usual clinical classification of DRS needs to be updated in order to match more accurately the underlying dysinnervation of the extra ocular muscles and to illustrate the continuum that exists between the various forms. This review aims to summarize the major findings about DRS and to guide the clinician in the surgical management of this particular form of strabismus.

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1. Introduction

The Duane retraction syndrome (DRS) has driven a lot of research in the last decade. Tremendous information about the DRS pathogenesis, its clinical presentation, its treatment and other various aspects of this condition have been reported in the scientific literature. An analysis of the new available information and of the corresponding major findings could lead to a better understanding of the pathogenesis of this particular form of strabismus. Advances in embryogenesis, in genetics and in electromyographic characteristics, plus the visualization of the oculomotor nerves by cerebral imaging lead to accept DRS as being a unilateral or bilateral congenital anomaly of the 6th cranial nerve nuclei with aberrant innervations by supply from the 3rd cranial nerve. Additional information about the underlying innervational deficit has been recently obtained by eye movement recordings. Careful clinical evaluation of the eye motility coupled with all collected data leads to update the previous classification of the different subtypes of DRS in order to guide the surgical management.

Eye movement recording represents a window into the brain as both neural and mechanical factors determine human eye move-

ments (Leigh & Zee, 2006). Therefore, in this particular form of strabismus, this technique provides new insight into the neural control of eye movements. The specific anatomical and physiological substrate of DRS makes it an ideal candidate for studying the binocular control of saccades, brain adaptation and provides a challenge for testing the existing control system models. Indeed, in contrast with comitant strabismus, binocular vision is preserved in DRS. Indeed, the compensation by abnormal head posture allows binocularity in one field of gaze despite the severe eye motility deficit in the other field of gaze. The degree of sensorial binocular status plays an important role in the conjugacy of saccades (Kapoula, Bucci, Eggert, & Garraud, 1997). Therefore, unilateral forms of DRS give the opportunity to study the coupling and/or uncoupling of the two eyes (one sound eye and one affected eye) during eye movements (Yüksel, Optican, & Lefevre, 2005). Binocular recordings of horizontal saccades to and away from primary position brought precious information about the innervational command sent to the two eyes. The relationship between saccade amplitude of the affected eye and the sound eye was linear for all directions of eye movements implying a close coupling between the two eyes. In addition, this condition provides another window on the adaptive processes that are required to control the abnormal eye plant. The comparative study of saccades in monocular versus binocular viewing conditions enabled to show that monocular adaptation was possible only for the step of innervation (i.e. controlling the

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final eye position) but not for the pulse of innervation (i.e. controlling the saccadic gain), even though the peculiarity of DRS type I offered clear advantage for separate pathways of control for the two eyes. This set of data allowed us to propose a model of common pathway for the pulse of innervation for the two eyes with separate pathways of command for the step of innervation (Yüksel, Orban de Xivry, & Lefevre, 2008). In parallel to yielding insights into brain function, eye movements also provide some information about the condition itself. For instance, eye movement recording in unilateral DRS during periods of monocular versus binocular vision allows testing for the presence of some residual innervation in the affected 6th nerve and for the type of transfer of innervation from one eye to the other according to the viewing condition. In addition, the integrity of the abducens interneurons could be inferred from the normal behavior of the sound eye toward the affected-side gaze.

Most of DRS patients compensate well for the disorder and do not require further management. Standard management of DRS may in some cases involve *eye muscle surgery*. Surgery does not eliminate the fundamental abnormality of innervation and no surgical technique has been completely successful in restoring full normal eye movements in DRS patients. The success rate in eliminating an abnormal head position is above 80%. Results are stable for at least 8.75 years after surgery (Barbe, Scott, & Kutschke, 2004). Surgery does not normalize horizontal motility. Only transposition procedures may in selective cases improve abduction (away from the nose = outward rotation of the globe), with some sacrifice on adduction (toward the nose = inward rotation of the globe). Lateral rectus fixation into the lateral orbital wall with augmented transposition of vertical muscles with vessel sparing technique is promising for treating severe DRS associated with abnormal up or downshoots on adduction (Rosenbaum, 2004). Undercorrection and overcorrection may occur if the particular mechanical and innervational aspects of DRS are not taken into account.

In order to optimize DRS management, diagnosis has to be made based on precise evaluation of the clinical signs. The use of additional clinical tests as forced duction, magnetic resonance imaging, saccade recording and modeling of the saccadic behavior of DRS may contribute not only to better understand the pathology but also guide the clinician in the daily practice management and in the surgical planning. In view of various aspects of the pathogenesis, a new form of classification is proposed.

2. General characteristics

Duane retraction syndrome (DRS) is a well-recognized clinical entity since more than a century. Stilling (1887), Turk (1896) and Alexander Duane (1905) are the early describers of this particular form of strabismus. In European literature the retraction syndrome is appropriately referred to as the Stilling–Turk–Duane syndrome.

DRS is rare in the general population with an incidence of about 0.1%. Prior reviews of DRS, comprising mostly unilateral cases, report a 1–4% proportion of all strabismus cases. The syndrome is usually unilateral and sporadic; however, numerous cases of familial transmission, mostly bilateral with an autosomal dominant inheritance pattern, have been reported (Sevel & Kassir, 1974). A family of 118 members in three generations, including 25 living members affected with DRS in an autosomal dominant pattern has been studied (Chung, Stout, & Borchert, 2000). Studies of DRS have been published in almost all areas of the world, and no particular race or ethnic group presented a predisposition for the syndrome. The majority of studies pointed out up to 60% predominance of the syndrome among females. This observation led to the hypothesis that the gene was partly sex-limited. The left side predominance has been cited in all the studies of DRS over the last

century. When all major studies were gathered, over a total number of 835 patients, 59% were left eye affected, 23% were right eye affected and 18% were bilateral. If bilateral cases were eliminated, over a total number of 680 patients, 72% presented a left eye involvement. There has been no explanation found for this preponderance of left eye involvement (DeRespinis, Caputo, Wagner, & Guo, 1993). Over a total number of 471 patients grouping six major studies, it appeared that hypermetropia greater than +1.50 diopter (D) was more frequent in DRS (71%). Myopia and emmetropia appeared in relatively equal amounts (15% and 14%, respectively). Anisometropia greater than +1.00 diopter in sphere, cylinder or both was found in approximately 23% of the 471 patients gathered from the major six studies (range of 14–40%). The range of amblyopia in Duane's syndrome was from 3% to 25%, with the weighted average being 14% among studies. Amblyopia was mainly due to strabismus and not to anisometropia (DeRespinis et al., 1993). Seventy cases of Duane's syndrome are summarized with particular attention to the prevalence of anisometropia and amblyopia (Tredici & von Noorden, 1985). They found a 17% prevalence of anisometropia and a 3% prevalence of amblyopia among these patients. Amblyopia and anisometropia do not seem more common in Duane's syndrome than in the general population. Fixation preference usually corresponds to the dominant eye based essentially on strabismic dominance, and/or the visual acuity. However, a few cases of fixation preference for the affected eye have been reported (Khan & Oystreck, 2006). DRS is associated with various ocular and nonocular malformations (15–50%) according to the time of development of the ocular and nonocular structures involved (DeRespinis et al., 1993).

3. Central nervous system anomalies

Because DRS is a benign disorder, autopsy subjects are rarely available. Matteucci was the first to report **hypoplastic abducens nucleus with absent 6th nerve** on the affected side in one *DRS type I* patient (Matteucci, 1946). The lateral rectus muscle was described fibrotic and the medial rectus muscle hypertrophic. The peripheral innervations of the lateral rectus muscle were not discussed, nor were the terminal branches of the oculomotor nerve followed. Two other autopsy reports have brought neuroanatomical evidence of high importance by complete intracranial and orbital pathologic examination of two cases of DRS in which the clinical findings were well documented (Hotchkiss, Miller, Clark, & Green, 1980; Miller, Kiel, Green, & Clark, 1982). The first case was bilateral *DRS type III* and the second was described as *DRS type I*. Clinical appearance of the motility of the studied subjects is sure enough *DRS type III* for the first report, but is more likely to be a *DRS type II* for the second report. Indeed, the limitation in *adduction* is more severe than the limitation in *abduction*. Postmortem examination of the brainstem and the posterior parts of the orbits revealed bilateral hypoplasia of the abducens nuclei and the abducens nerves. The abducens nucleus contained **no motor neuron cell bodies** at levels the abducens nuclei normally occupy, but did contain **several small cell bodies compatible with internuclear neurons**. No intra-axial fibers referable to the 6th cranial nerve could be identified within the brainstem. Both **oculomotor nuclei and nerves were normal** at the level of the ciliary ganglion. The **inferior division of the oculomotor nerve divided into several branches penetrating the inferior medial aspect of the lateral rectus muscle**. Sections through the lateral rectus muscle show healthy, well-formed muscle bundles in areas innervated by fibers from the third nerve. The remaining muscle mass was poorly innervated and showed fibrosis. The medial rectus was normal in size and structure. These data brought relevant information to explain major electromyographic findings (Scott & Wong, 1972).

Regarding these elements, it appears that development of the lateral rectus muscle may proceed even if its usual nerve supply is defective (hypoplasia of the 6th nerve nucleus) because of the presence of a substitute nerve branch coming from the oculomotor nerve. This extra branch may derive from the superior or inferior division of the oculomotor nerve. The abducens and the oculomotor nerves are closely associated as they pass through the cavernous sinus and particularly as they enter the orbit through the two heads of the lateral rectus muscle. Anastomoses between the two nerves in the cavernous sinus and the orbit provide theoretical opportunity for intermingling of their axons (Hoyt & Nachtigaller, 1965).

4. Embryogenesis

The myofibers of extra ocular muscles (EOMs) of the eye are developed by a condensation of the mesoderm around the eye whereas muscle connective tissue cells arise from neural crest. Oculomotor nerves grow out from the brain into their respective primordial muscle condensations some time after the latter have been formed. When the embryo is 7 mm long, the EOMs form one mass, which is supplied by only the third nerve. When the embryo is 8–12 mm long, that is, when the fourth nerve and the 6th nerve arrive, this mass divides into separate muscles. The oculomotor nerve first appears at the 7–8 mm stage, then the abducens at the 8–9 mm stage and finally the trochlear at the 10–12 mm stage. It is conceivable that, through disturbing influences of unknown origin, branches of the third nerve remain or come into contact with the part of the muscle mass which is later to become the lateral rectus. This occurs in the compensation for an aplastic or absent abducens nerve (Hoyt & Nachtigaller, 1965). Bremer proposed that absence of abducens nerve in the human is due to a relative delay in development of the primordial muscles; this allows the abducens fibers sprouting from the brainstem to turn caudally in response to the “attraction” of the postotic musculature. Subsequently, the developing lateral rectus muscle is annexed by another nerve, the oculomotor nerve. The caudally directed abducens fibers then disappear along with the postotic mesoderm, leaving no trace of their original emergence from the brainstem. Latest studies emphasized the critical role of the protein @2-chimaerin in the developmental function in ocular motor axon path finding (Miyake et al., 2008).

Given the evidence that DRS results from a maldevelopment of the abducens nerve (cranial nerve VI) and that DRS is associated with other anomalies in some cases, the syndrome is thought to reflect a disturbance of normal embryonic development. Either a genetic factor or an environmental factor may be involved when the cranial nerves and ocular muscles are developing *between the 4th and the 8th week of gestation*.

Studies of sporadic forms of DRS showed 10–20 times greater risk for having other congenital malformations divided in mainly four categories: skeletal, auricular, ocular and neural (Pfaffenbach, Cross, & Kearns, 1972). The skeletal abnormalities involved the palate and vertebral column. The auricular malformations included the external ear, the external auditory meatus and the semicircular canals. Ocular defects concerned the extra ocular muscles and the eyelids including ocular dermoids. Neural defects involved the third, fourth and 6th cranial nerves. Some other syndromes are described to be associated with DRS; Okihiro syndrome (forearm malformation and hearing loss), Wildervanck syndrome (fusion of neck vertebrae and hearing loss), Holt-Oram syndrome (abnormalities of the upper limbs and heart), morning-glory syndrome (abnormalities of the optic disc or blind spot), and Goldenhar syndrome (malformation of the jaw, cheek, and ear, usually on 1 side of the face). Given those clinical data, disturbance between the

fourth to tenth weeks of embryogenesis seems most obvious and could explain the various nonocular and ocular abnormalities in combination with Duane's syndrome. A teratogenic event during the second month of gestation seems to cause most ocular and extraocular abnormalities observed in combination with DRS. Thalidomide has been clearly reported as having a teratogenic effect.

5. Hereditary and genetic factors

Both genetic and environmental factors are likely to play a role in the development of Duane syndrome. The majority of Duane syndrome cases are sporadic in origin with only approximately 2–5% of patients showing a familial pattern (running in families), and large families are rarely reported. Both dominant forms and recessive forms of DRS have been documented. In some families with dominant DRS, the disease skips a generation (reduced penetrance) and ranges in severity (variable expressivity). Most familial cases are not associated with other anomalies. Kirkham was the first to note a genetic link between the cleft palate, Klippel–Feil anomaly, perceptive deafness and DRS. These anomalies seemed to be manifestations of a pleiotropic gene inherited in an irregularly dominant manner (Kirkham, 1969; Kirkham, 1970a, 1970b). Studies of monozygotic twins have added some confusion to the genetics of DRS. Some reported concordant cases (Hofmann, 1985), some reported discordant cases (Kaufman, Folk, & Miller, 1989; Rosenbaum & Weiss, 1978) and one study reported monozygotic twins with unilateral DRS, each with the opposite eye affected, described as “mirror images” (Mehdorn & Kommerell, 1979). There is currently no test that can determine whether a patient has a hereditary form.

Genetic linkage studies of a large family with DRS established the location of a DRS gene on chromosome 2. Although a genetic cause of DRS has long been accepted, these studies were the first to show a statistically significant linkage. Only one genetic locus for isolated DRS has been established by linkage analysis: the DURS2 locus on 2q31 (Appukuttan et al., 1999; Evans, Frayling, Ellard, & Gutowski, 2000). Cytogenetic results (a study of chromosomes) of individuals with Duane syndrome have, in rare cases, shown abnormalities that suggest that there may be more than one gene responsible for causing DRS. Deletions of chromosomal material on chromosomes 4 and 8, and the presence of an extra marker chromosome thought to be derived from chromosome 22 have been documented in DRS individuals.

Observations led to the feeling that various internal stimuli during embryogenesis determine uni- or bilaterality, sidedness and degree of expression. The involved gene was proposed to be incompletely penetrant with variable expressivity. Identification of the genes mutated in inherited DRS can provide insight both into the cause of the disorder and the molecular pathways essential to ocular motoneuron and axon development. Using this approach several mutations in the transcription factor *SALL4* have been identified to cause DRS in association with variably penetrant radial ray deformities and deafness gene defects that result in Duane-radial ray syndrome (DRRS), a disease that was found to map to Chromosome 20 (Engle, Andrews, Law, & Demer, 2007). The finding that the DRS phenotype maps to the DURS2 locus has provided an opportunity to define further the DURS2-linked DRS phenotype. Comparison of the clinical and MRI findings within DURS2-linked DRS families and the sporadic DRS provide guidance for future examinations of the role of the DURS2 gene in ocular motor development. DURS2-linked DRS has been reported to be a diffuse congenital cranial dysinnervation disorder not limited to the abducens nucleus and 6th cranial nerve (Demer, Clark, Lim, & Engle, 2007a). Similar to congenital fibrosis of the extra ocular muscles (CFEOM), DRS may be classified as strabismus, under the subclassification of

incomitant strabismus and extraocular muscle fibrosis syndromes. Although the term muscle fibrosis suggests that syndromes under this heading are primary disorders of muscle, evidence suggests that DRS (and other syndromes under this heading, including CFE-OM) may be primary disorders of nerve innervation. A most recent study reported that @2-chimaerin has a critical developmental function in ocular motor axon path finding because expression of mutant @2-chimaerin constructs in chick embryos resulted in failure of oculomotor axons to innervate their target extra ocular muscles (Miyake et al., 2008). Genetic studies are promising for the future and new classifications might be conducted in view of innovative genetic findings.

6. Clinical description of Duane retraction syndrome (DRS)

The detailed clinical description of the oculomotor disorder has been reported with the following manifestations:

- (1) complete, or less often partial, *absence of outward movement (abduction)* of the affected eye (Fig 1A);
- (2) partial, or rarely complete, *deficiency of inward movement (adduction)* of the affected eye (Fig 1B);
- (3) *retraction* of the affected eye into the orbit when it is adducted (Fig 1B);
- (4) *partial closure of the eyelids* (pseudoptosis) of the affected eye when it is adducted (Fig 1B);
- (5) a *sharply oblique movement* of the affected eye, either down and in (downshoot) or up and in (upshoot, Fig 1C), when it is adducted;

- (6) paresis, or at least *marked deficiency of convergence*, with the affected eye remaining fixed in the primary position while the other eye is converging; (Fig 1D);
- (7) abnormal head posture is adopted to search for the direction of gaze where there is no misalignment of the two eyes in order to obtain binocularity. Longstanding torticollis (since birth) leads commonly to *craniofacial asymmetry* (Fig 1E). For clinicians, the sign of facial symmetry is precious to differentiate congenital from acquired forms of motility disorder.

In the clinical setting, the principal difficulties in differential diagnosis arise as a consequence of the very early age at which patients with this condition first present. The clinician must be very careful in examining abduction and adduction, as well as in looking for any associated palpebral fissure changes or head postures, when attempting to determine whether what often presents as a common childhood squint is, in fact DRS. Some cases are challenging because the palpebral signs are uncertain. Some additional clinical signs have to be pointed out for deciding whether any abduction limitation is the result of DRS and not a consequence of abducens cranial nerve palsy. The following clinical signs evoke DRS and not abducens nerve palsy:

- (1) Despite the severe limitation of abduction, there is no severe eye misalignment in primary position in DRS (Fig 2A) contrary to 6th nerve palsy which results in large angle of esotropia in primary position (Fig 2B).
- (2) Deficiency of abduction is less pronounced in elevation and depression in DRS (Fig 3A) while the limitation of abduction remains the same in elevation and depression in 6th nerve palsy (Fig 3B).

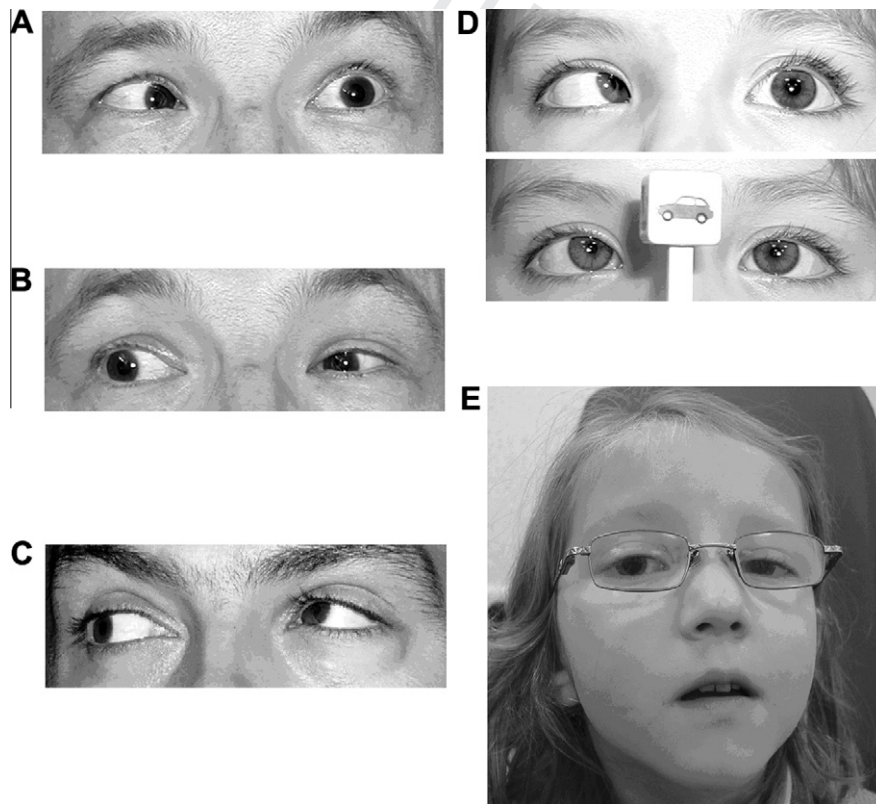


Fig. 1. (A) Gaze to the left (affected-side gaze) of patient JLB with unilateral DRS type I. Left eye is affected. (B) Gaze to the right (sound-side gaze) of patient JLB with unilateral DRS type I. Left eye is affected. There is partial deficiency of inward movement (adduction) of the affected eye with retraction into the orbit and partial closure of the eyelids when it is adducted. (C) Gaze to the right (sound-side gaze) of patient LT with unilateral DRS type I. Left eye is affected. There is a sharply oblique upward movement of the affected eye when it is adducted, so-called "upshoot". (D) Patient PM shows unilateral DRS type I. Left eye is affected (top). Vergence of the sound eye (right eye) is complete and vergence of the affected eye (left eye) is limited (bottom). (E) Patient JB turns the head to the left for searching eye alignment in right gaze. Facial asymmetry is noticeable with half of the face less developed on the left side. Diagnosis is unilateral DRS type I on the left side.

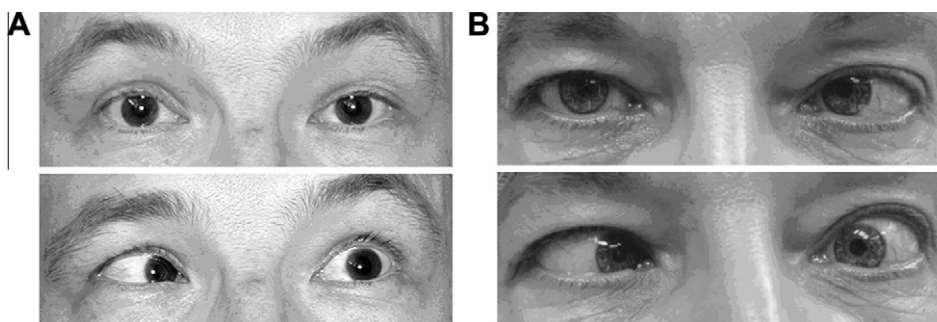


Fig. 2. (A) Patient JLB is orthotropic in primary position with the head straight (top), despite severe limitation of abduction of the left eye (bottom). Diagnosis is DRS type I on the left eye. (B) Patient FL is esotropic in primary position (top) secondary to absence of abduction of the left eye (bottom). Diagnosis is complete 6th nerve palsy secondary to neurosurgical tumor excision for therapeutical purpose.

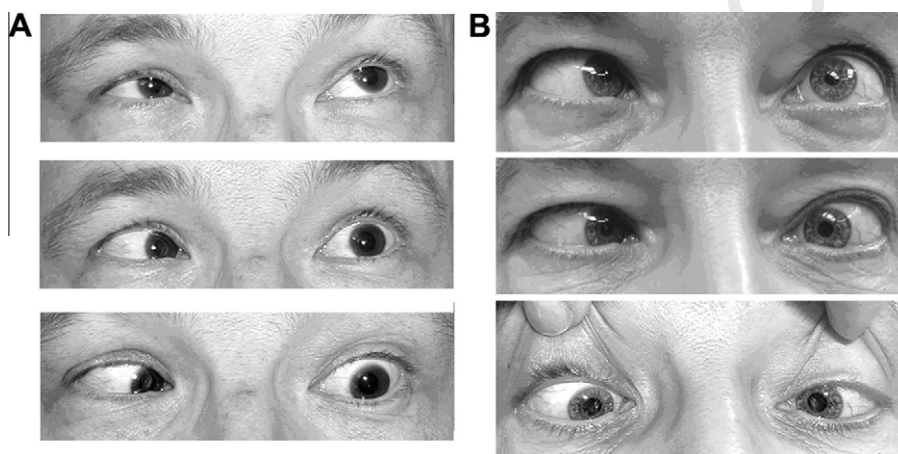


Fig. 3. (A) Patient JLB presents DRS type I of the left eye with severe limitation of abduction in horizontal gaze to the left (center). The limitation of abduction improves when the eye looks to the left and up (top) and when the eye looks left and down (bottom). (B) Patient FL presents complete 6th nerve palsy of the left eye with complete absence of abduction in horizontal gaze to the left (center). The limitation of abduction does not improve when the eye looks to the left and up (top) and when the eye looks left and down (bottom).

Disorders similar in clinical presentation to DRS have been described as a result of trauma (Duane, Schatz, & Caputo, 1976), orbital surgery (Sood, Srinath, & Krishnamurthy, 1975), pterygium excision surgery (Khan, 2005), following localized infection (Murthy, 2008), neoplasm (Kivlin & Lundergan, 1985) or inflammation of the orbital soft tissue and/or of the extra ocular muscles leading to consequent mechanical restrictions of eye movement (Kargi et al., 2005; Moorman & Elston, 1995; Osher, Schatz, & Duane, 1980). Neurogenic causes that mimic Duane-like syndrome have also been reported in the literature after surgery on the 5th cranial nerve (Smith & Damast, 1973) or secondary to pontine glioma (Akiko, Masato, Tetsuro, & Keichi, 2003). The retraction of the globe was the main common picture and occurred either in adduction or in abduction associated to horizontal motility limitation. But in all cases, the underlying cause was different from DRS and therefore the name “pseudo-Duane’s retraction syndrome” was preferred.

“Vertical retraction syndrome” indicates the presence of retraction movements in vertical gaze (Khodadoust & von Noorden, 1967; Prakash & Menon, 1981; Spielmann, 1988). Because of their analogy with Duane’s syndrome, the vertical restriction syndromes have sometimes been called “vertical Duane’s syndrome.” This terminology should be avoided and substituted by the term “pseudo-vertical” Duane’s syndrome to avoid confusion.

It is however clear that retraction syndrome is a wide spectrum of cranial dysinnervation that may be spread to cranial

nerves other than the abducens. DRS should be utilized only when the lateral rectus is concerned. The understanding of the underlying mechanism is essential to avoid misdiagnosis and confusion.

7. Electromyographic findings

From as early as 1900–1957, numerous investigators reported a spectrum of anatomical findings when operating on extra ocular muscles (Breinin, 1957; Gobin, 1972). Studies led to the conclusion that DRS was a local, purely myogenic phenomenon. Posteriorly or multiply inserted medial rectus muscle and/or fibrotic, inelastic lateral rectus muscle have been widely described. It was believed that the cause of abduction deficiency was the fibrosis of the lateral rectus muscle and that limitation of adduction was due to the abnormal posterior insertion of the medial rectus muscle or to adhesions between the medial rectus muscle and the orbital wall. Other surgeons found no macroscopic anomalies of both horizontal rectus muscles and assumed a faulty action of the vertical muscles or a deficiency of the check ligaments. All these findings could explain some of the characteristics of the ocular motility but failed to explain all the components of the clinical entity.

Electromyographic investigations allowed the recording of the electrical activity in human extra ocular muscles for different eye

positions. Gaze-directed extraocular muscle innervations were recorded. Breinin (1957) used *electromyography* and was the first to describe the absence of potentials of the lateral rectus muscle in abduction, but the presence of action potentials in adduction (Breinin, 1957). This finding was the evidence of *co-contraction* of the medial and lateral rectus muscles in adduction and was made responsible for the observed globe retraction in adduction. There were many other electromyographic studies to follow. The action potentials of the lateral rectus muscles ranged from no activity during abduction to essentially equal activity in adduction versus abduction. Medial rectus activity was apparently normal. By 1974, Huber gathered all electrophysiological information to conclude that a **paradoxical innervation of the lateral rectus muscle** of the affected eye represents the pathogenic principle of all the retraction syndromes (Huber, 1974). The consequent disorder of the agonist–antagonist interaction between the medial and lateral rectus muscles has been explained to be responsible for the observed secondary anatomical alterations in the muscles. With regard to the various electromyographic patterns, **Huber's classification** system groups DRS into three entities; type I (limited abduction with normal to near normal adduction), type II (limited adduction with normal to near normal abduction), type III (limited abduction and adduction). This scheme has been widely accepted for clinical and electromyographical classification. Over a total number of 340 patients gathering five major studies, a three to one preponderance of DRS type I (according to Huber's classification) was noted: DRS type I (78%), DRS type II (7%) and DRS type III (15%) (DeRespinis et al., 1993). **A modification of Huber's classification** was proposed by Ahluwalia, Gupta, Goel and Khurana (1988). It brought many practical clinical aspects by **including the deviation noted in the primary position of gaze** in each of the three groups. It is only relevant for DRS type I because DRS types II and III always have exotropia in primary position (pp). The proposed classification is as follows: DRS type IA (esotropia in pp), DRS type IB (exotropia in pp) and DRS type IC (orthotropia in pp).

The electromyographic classification of DRS has been widely discussed and completed. Different types of anomalous lateral rectus muscle innervations in DRS have been recorded since Huber. Even in the subgroup of DRS type I, it appeared to be various innervations patterns. This information should be brought to light because its implication in the prognosis of the surgical management is very important. A large review of different patterns of the electrical activity measured in the affected lateral rectus (LR) depending on the gaze has been extensively described by Jampolsky (1999). Aoki and Mukuno (1989) reported the existence of three EMG subtypes in clinical DRS type I. Mizukawa and colleagues have recently described two additional new types of electromyographic recordings (Mizukawa, Kimura, Fukai, & Tabuchi, 2004). These observations bring some new information correlated with subgroups of DRS type I and match better the clinical pattern in DRS type I with various abnormal head postures and different deviation of the eyes in primary gaze.

In view of the tremendous information that the electromyography has provided, horizontal limitation of abduction and adduction to varying degrees has been well explained by the abnormal innervation of the lateral rectus, so-called *paradoxical innervation*. Medial rectus muscle innervation was always normal. The globe retraction and the narrowing of the lid fissure in adduction have been accepted to be secondary to the *co-contraction of both horizontal muscles* in adduction. The rearward force to generate globe retraction was measured, and both the co-contraction theory and the lateral rectus fibrosis theory seemed to be capable of explaining the phenomenon (Scott & Wong, 1972). Explanations for upshoots and downshoots of the affected eye in adduction have been strongly disputed between mechanical and anomalous inner-

vation theories. The *“bridle effect”* in the horizontal muscles secondary to fibrosis and co-contraction would create a certain amount of slippage toward elevation or depression (Miller, 1989). This theory was widely supported by the success of surgical weakening procedures and intramuscular injections of xylocaine performed on the *horizontal* muscles (Magoon, Cruciger, Scott, & Jampolsky, 1982; von Noorden & Murray, 1986). In contrast, the same procedures performed on *vertical and oblique* muscles failed to eliminate these vertical abnormal movements. However, anterior views near the level of the rectus pulleys showed no evidence of horizontal rectus EOM sideslip, indicating that the downshoot was not due to a *“bridle effect”* during horizontal rectus co-contraction (Demer et al., 2007a). But, so much improvement in up or downshoot movements has been obtained by surgical procedures performed on horizontal muscles, one would imagine that even if the pulleys do not show sideslip, the restrictive phenomena may occur more anteriorly and concern the anterior insertions of the EOMs. Electromyography (EMG) has certainly clarified the nature of the lateral rectus muscle anomalous innervation but few misinterpretations and artifacts have led to some confusion concerning supplied innervation from the oculomotor nerve. The major problem with electromyographic studies consists in the uncertainty about the site of recording in the muscle fibers. This concerns especially the lateral rectus muscle which is composed of various zones of residual muscle fibers due to the innervation either by the supplying 3rd nerve, either by residual tiny 6th nerve fibers and zones of atrophy with fibroblastic tissue secondary to absence of any innervation (Scott & Wong, 1972). The waveform of the recording depends on the site of implementation of the needle. Moreover, there is no quantitative correlation between the amplitude of the signal and the range of the eye movement. Electromyographic recordings during a saccade show a large motor unit input. Studies measure the signal when the eye is maintained in an eccentric position. This does not represent the signal of innervation as the pulse and step signal sent to the eye muscle. Therefore eye movement recordings are interesting because they give more information about the motor command sent to the eye muscles. Indeed, the study of saccades infers information about the signal of innervations and the mechanical properties of the eye muscles. However, the information gathered by eye movement recordings does not give information about one extraocular muscle but concerns the resultant of the activity of all the extra ocular muscles during a particular gaze, thus it will usually prove very useful to combine a variety of recordings in different conditions in order to make sound conclusions.

8. Data from cerebral and orbital imaging

Magnetic resonance imaging (MRI) appeared to be a precious new tool to visualize the brain and the pathway of the cranial nerves over the past 20 years. Indeed, the new techniques offer high resolution images in a non-invasive way and the contribution of MRI to the clinical management of strabismus and complex oculomotor disorders has been undeniable. Motion-encoded magnetic resonance imaging (MRI) was recently used for the study of human extraocular muscle (EOM) function; local physiologic contraction and elongation (deformation) were quantified (Picciarelli et al., 2009).

The visualization of the abducens *nucleus* itself at a neuronal level remains unfeasible. But, the nerve can be explored at the pontomedullar level. MRI in cases of DRS type I, demonstrated the **absence of the abducens nerve** (Parsa, Grant, Dillon, du Lac, & Hoyt, 1998; Yüksel et al., 2005). This observation is illustrated by an axial-oblique reformatted T_2 -weighted image of the brainstem at the pontomedullar level of a subject presenting a unilateral form

of DRS type I on the right side (Fig 4). However, the variety of the presence of the abducens nerve in DRS was pointed out by one study (Ozkurt, Basak, Oral, & Ozkurt, 2003). These results must be interpreted with caution. Not only did they not observe the abducens nerve in one of the 16 eyes in a control group, but also there was no classification of the types of DRS patients. More recently, a study compared MRI findings of 23 DRS patients with a control group of 20 individuals. Results confirmed the absence of the abducens nerve on the affected side in all patients with DRS type I, mostly in all patients with DRS type III, while DRS type II was usually associated with normal 6th nerve (Kim & Hwang, 2005b; Yüksel et al., 2005). The most recent MRI study in DRS described two cases of DRS with absence of the abducens nerve in both cases. The classification of DRS reported one DRS type I and one DRS type II. The authors suggested that DRS type II could also be associated with abducens nerve aplasia. However, the patient classified DRS type II seems to be more intermediate between types IB and II. Indeed, in the patient described as DRS type II, even if adduction was more limited than abduction, the deviation in primary position was ortho to small angle exotropia which is more equivalent to the subgroup type IB. It is therefore essential to correlate MRI findings with clinical data. This heterogeneity of the results regarding the visualization of a partial or complete absence of the abducens nerve raises the question about the importance of the classification of the syndrome based on its pathogenesis. In fact, histological studies described above concerned only patients with DRS types I and III. DRS type II is extremely rare and therefore requires more cases than already reported for better understanding its innervational characteristics. An interesting report compared MRI findings in patients with congenital fibrosis of the extra ocular muscles (CFEOM = congenital ocular motility disorder that manifests as restrictive ophthalmoplegia with ptosis) and patients with synergistic divergence (variant of DRS); the oculomotor nerve was hypoplastic bilaterally, and the abducens nerve was absent on the side exhibiting synergistic divergence (Kim & Hwang, 2005a).

As to the **visualization of the peripheral abnormal innervations** by MRI, coronal T_1 -weighted magnetic resonance images of the orbits and heavily T_2 -weighted images in the plane of the cranial nerves were obtained in subjects with DRS linked to DURS2 locus on chromosome 2 (Demer et al., 2007a) and in subjects with Duane-radial ray syndrome (DRRS) caused by mutations in the transcription factor SALL4 (Demer, Clark, Lim, & Engle, 2007b). The lateral rectus is shown to be co-innervated by the third cranial nerve in both reports. DRS linked to DURS2 locus is described to be

associated with anomalies of many orbital motor nerves and structural abnormalities of all EOMs except those innervated by the inferior branch of the third nerve contrarily to DRRS for which the EOMs and pulleys were structurally normal in most subjects. Although MRI resolution is inadequate to confirm the presence of motor endplates in the LR, the inferior division of CN3 was reported to run consistently adjacent to the deep portion of the LR where CN6 normally enters and arborizes. LR muscles regional abnormalities were described in subjects with DURS2, in the form of hypoplasia and absent contractility in the deep portion of the EOM belly. Where present, CN6 was seen to enter the superior zone of the LR, whereas aberrant innervation from CN3 entered the inferior zone. This finding was reported as implying that the LR in DURS2 is a two-headed EOM, with each head separately innervated but joined to a common scleral insertion. This functional anatomic observation brings explanation to the previous electromyographic observations in DRS of evidence of two populations of LR motor units: the presumably normally innervated population activated during abduction, and an abnormally innervated population originally destined for the medial rectus (MR) (Scott & Wong, 1972). These two populations presumably represent the two zones of the LR visualized by MRI.

The cross-sectional area of extra ocular muscles (EOMs) in different directions of gaze (primary position, affected-side gaze, sound-side gaze) is illustrated by axial and coronal T_1 -weighted images of the orbits in one subject presenting unilateral DRS type I on the right side (Fig 5). Images were interpreted in correlation with the knowledge of the innervational input necessary in conjugate eye movements for which the abducens nucleus is the main actor and is the main cause of the disorder in DRS (Yüksel et al., 2005). In this way, MRI brought information about the paradoxical innervation of the affected lateral rectus in DRS. The first finding concerned the absence of atrophy of the lateral rectus muscle body in the affected eye in *primary position* where the eyes were aligned during constant fixation, despite the absence of innervation by the 6th nerve on that side. It is in accordance with other imaging studies of DRS type I. A denervated muscle usually atrophies. The LR muscle exhibits profound atrophy in *severe* abducens palsy (Kang & Demer, 2006). Indeed in *partial* abducens nerve palsy, the extra-ocular muscle size may not demonstrate significant muscle atrophy (Ozkurt & Aribal, 2007). The sparing of the LR in Duane syndrome from denervation atrophy despite absence of normal abducens innervations suggests existence of alternative LR innervation. The importance of this observation is illustrated by a report of an unusual case of Duane's syndrome who presented with recurrent, large-angle esotropia and uncharacteristic atrophy of the lateral rectus muscle on magnetic resonance image (MRI) scan (Silverberg & Demer, 2001). The atrophy of the lateral rectus muscle was explained by the presence of a skull base meningioma which presumably was responsible for compression of anomalous branches of the oculomotor nerve. Imaging of LR by high-resolution MRI thus appears to be a useful diagnostic tool for discriminating Duane syndrome type I from chronic abducens palsy. It might be of particular clinical use in children, and/or in challenging clinical patterns. The second finding concerned the visualization of LR and MR co-contraction of the affected eye during sound-side gaze movements. Indeed, the cross-sections of the muscle body of the lateral and the medial recti are equally large without any elongation of the lateral rectus muscle indicating a co-contraction phenomenon. This brought an indirect evidence of anomalous innervation of the affected lateral rectus by the ipsilateral third nerve. The absence of LR atrophy is therefore explained by some other innervation arising from the oculomotor nerve which prevents the LR from denervation atrophy. Since then, new imaging studies have reported direct visualization of the co-innervation of the affected lateral rectus muscle by branches of the oculomotor



Fig. 4. Axial-oblique reformatted T_2 -weighted image of the brainstem at the pontomedullar level in one subject presenting unilateral DRS type I on the right side. Right arrow: left 6th nerve at its emergence from the inferior pons in the subarachnoid space. Left arrow: clear absence of the 6th nerve at the same level. Adapted from Yüksel et al. (2005).

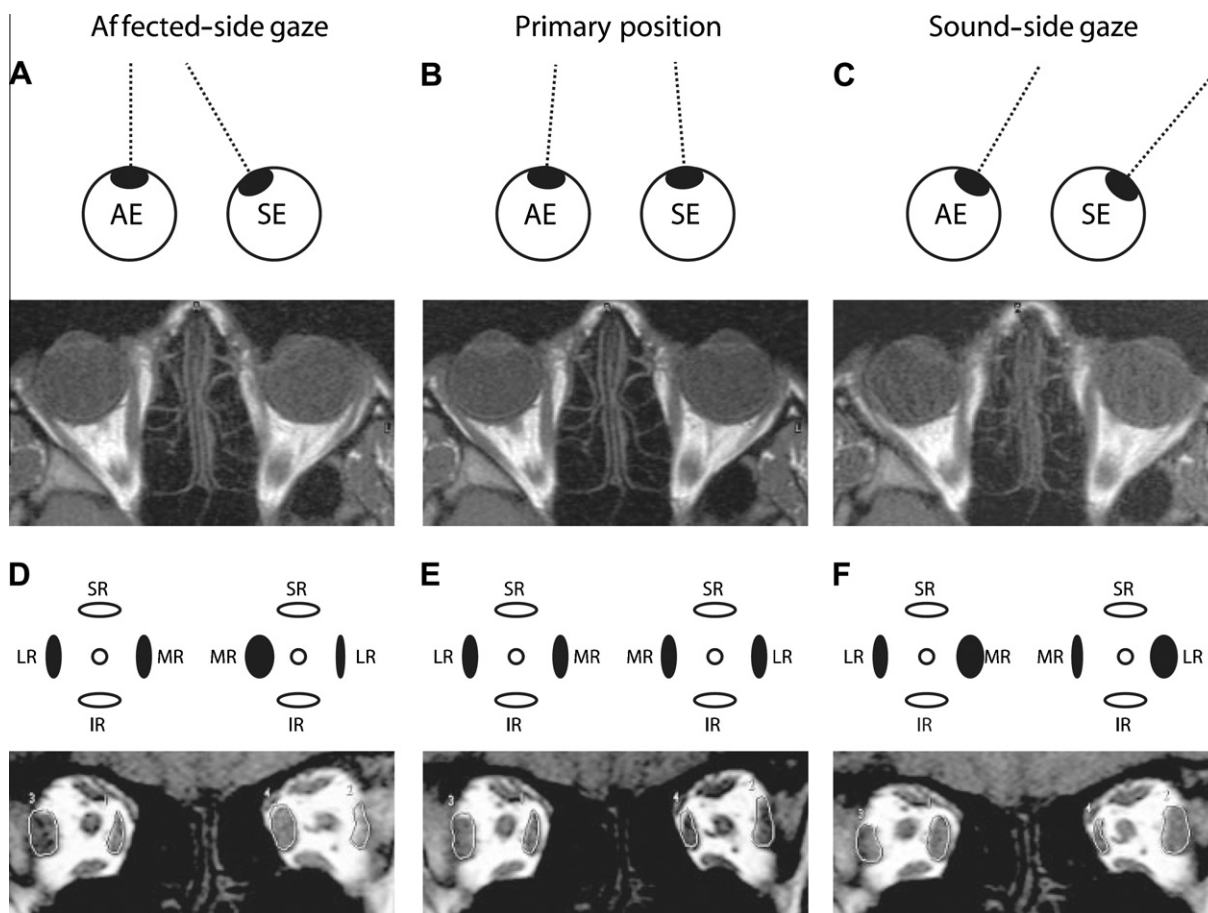


Fig. 5. Axial (A–C) and coronal (D–F) T_1 -weighted images through the orbits in one subject presenting unilateral DRS type I on the right side, obtained during constant fixation to affected-side gaze (A and D), in primary position (B and E), and to sound-side gaze (C and F). The contour of the EOMs was manually drawn on coronal views through the midline portion of the EOMs to visualize the relative movements of the globes and the relative sizes of the EOMs in each eye, in each direction of gaze. Adapted from Yüksel et al. (2005).

nerve. Comparison of these findings with the results of orbital imaging in other fibrosis syndromes (CFEOM) raises the question of including DRS in what would be called in more general way dysinnervation syndromes.

In conclusion, the high performance of the new imaging techniques by MRI certainly confirmed the maldevelopment of the abducens nerve in DRS and showed the compensatory innervation by the third nerve at a peripheral level. In this regard, MRI became an extremely precious tool for guiding the diagnosis and the management of difficult clinical features of oculomotor disorders. However, information about the brainstem circuitry at a neuronal level still remains impossible. Therefore, the adjunction of other techniques is useful. Eye movement recordings are an additional tool for understanding the underlying pathogenesis of DRS.

9. Data from eye movement recordings

A technique that could provide quantitative information about the strength of an extraocular muscle would be a useful addition to our clinical evaluation of patients with strabismus. Information would be available to assist the diagnosis in difficult cases and aid in management decisions. Direct measurements of muscle force are difficult to perform quantitatively; they are usually not possible in the paediatric age group and not comfortable in adult patients. In contrast, eye movements can be measured relatively easily and accurately with equipment available in many hospitals and medical centers.

Eye movement recording is a non-invasive technique that has given valuable information about the neural control of movement (Clarke, Ditterich, Druen, Schonfeld, & Steineke, 2002; Collewyn, van der Mark, & Jansen, 1975; Leigh & Zee, 2006; Robinson, 1963). Saccades are fast eye movements (up to $500^\circ/\text{s}$) that enable us to rapidly redirect our line of sight (fovea) toward the object of interest (Leigh & Zee, 2006). Saccades are characterized by a consistent relationship between their peak velocity and their amplitude, called the *main sequence*. Given that these relationships are all fairly stereotyped, one can use quantitative measurements of saccades to assess the function of the oculomotor system.

The kinematics of a saccadic eye movement is directly related to the force produced by extra ocular muscles and is thus an indicator of the strength of the muscles and their innervation. Therefore, the measurement of saccadic movements can provide an objective test to evaluate rectus muscle function. Moreover, it gives insight to central oculomotor organization. Many previous studies of DRS have provided qualitative descriptions of eye movements and involved a mix of all types of patients with DRS (types I–III). Nevertheless, in most studies, the properties of saccades were analyzed without making any distinction between centrifugal and centripetal movements, thus ignoring the manifest asymmetry in DRS. Most studies used low resolution techniques, such as electro-oculography (Gourdeau, Miller, Zee, & Morris, 1981; Metz, Scott, & Scott, 1975; Nemet & Ron, 1978; Prieto-Diaz, 1985). Moore, Feldon and Liu (1988) were the first to perform high-resolution recordings in two patients with DRS type I. In general, their findings supported

the hypothesis that DRS results from a central reorganization of the ocular motor function in the brain stem. However, they reported no differences between the dynamic characteristics of adducting saccades in the affected eye and those of adducting or abducting saccades in the sound eye, which contradicted all previous reports. This unusual finding is probably due to the pooling of centrifugal and centripetal movements in their data analysis. In general, all studies reported marked reduction in abduction saccadic velocity in type I Duane's syndrome. This is explained by the ocular electro-

myographic evidence of lack of muscle activity or recruitment of the lateral rectus muscle on attempted abduction. However, the inability to abduct the affected eye might be due in part to restriction by stiff medial tissues. This can be tested by force generation tests (Scott, 1971, 1975). Adduction saccadic velocities were moderately decreased. Ocular electromyography indicated that the medial rectus recruits and inhibits normally in Duane's syndrome. It was suggested that the reduced saccadic velocity on adduction is due to the co-contraction. This differentiates type I Duane's syn-

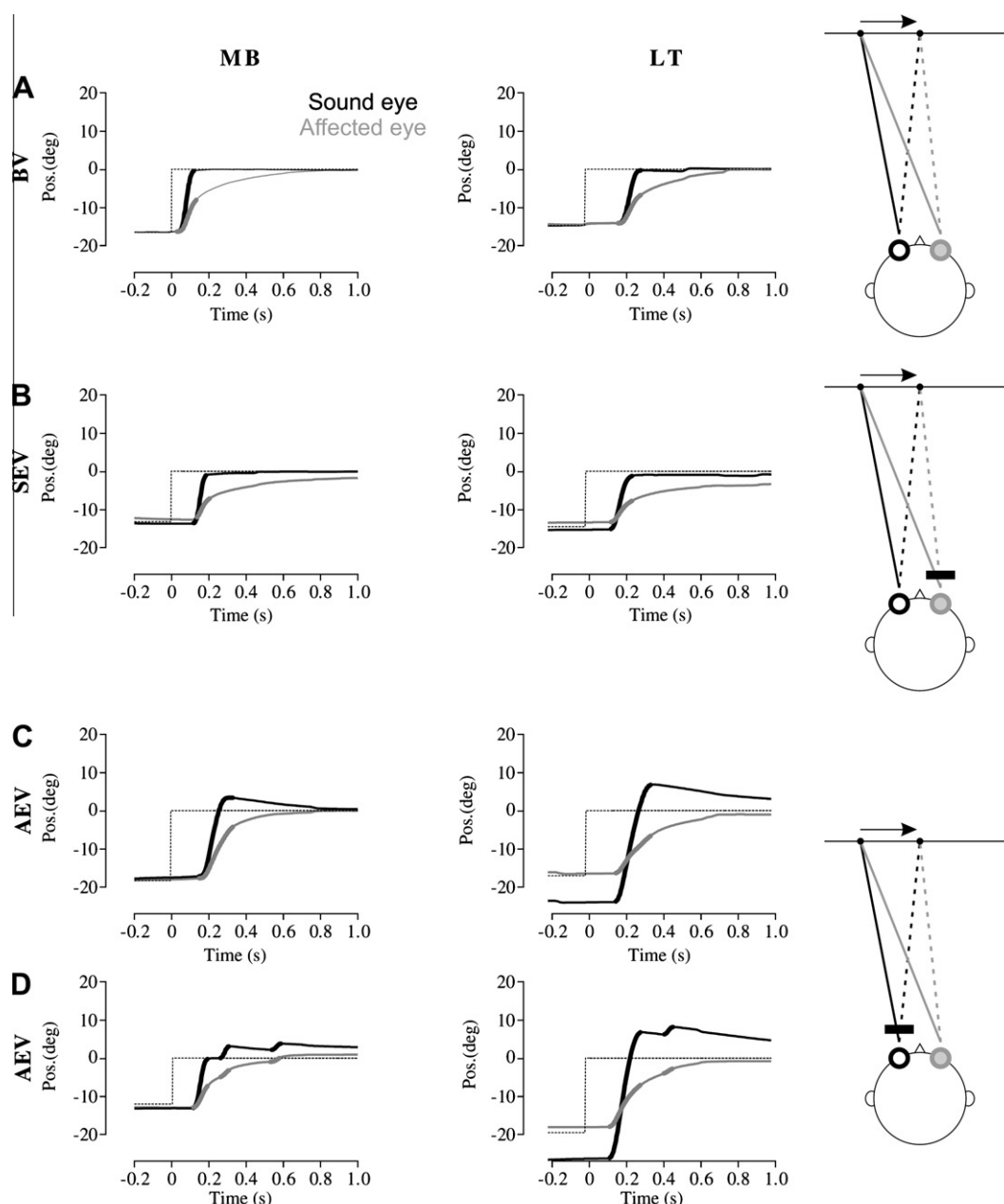


Fig. 6. Typical traces of centripetal eye movements toward the affected-side gaze, recorded with the search coil technique, for two subjects and in different viewing conditions (BV, SEV, AEV). Positive horizontal eye position corresponds to the affected-side gaze. Negative horizontal eye position corresponds to the sound-side gaze. (A) A typical binocular viewing (BV) recording for subject MB and LT. (B) A typical sound eye viewing (SEV) recording for subject MB and LT. (C) A typical affected eye viewing (AEV) recording for subject MB and LT with behavior of saccadic gain >1. (D) A typical AEV recording for subject MB and LT with a staircase behavior. The diagrams on the right part of the figure illustrate the target movement in centripetal direction from sound-side gaze (left on the diagram) toward the affected-side gaze (right on the diagram). Subject fixates the target in an eccentric position (left dot). Target is extinguished and appears in the center fixation position (right dot). The task induces centripetal abducting saccades for the affected eye and centripetal adducting saccades for the sound eye. Search coils measure eye position of the two eyes simultaneously. Viewing conditions include; BV = binocular viewing (both eyes open), AEV = affected eye viewing (sound eye occluded) and SEV = sound eye viewing (affected eye occluded). Subjects used the viewing eye to track the target while eye movements were measured simultaneously in the viewing and the non-viewing eye. The eye patch is represented by a black rectangle lying before the occluded eye. Adapted from Yüksel et al. (2005).

drome from lateral rectus palsy. In one DRS type I patient, horizontal saccades were measured before and after lateral rectus recession of the involved eye (Metz, 1983). Abduction saccades were unchanged, while adduction saccades improved to normal. The lateral rectus muscle, which had been co-contracting on adduction, had less effect following recession, with resultant improvement in the speed of nasal movements. The importance of identifying anomalous co-contraction of the lateral rectus muscle before planning an operative procedure has been pointed out (Blodi, Vanallen, & Yarbrough, 1964). Indeed, the results of transposition surgery of the vertical muscles toward the lateral rectus muscle seem unpredictable and present a high percentage of overcorrection.

Systematic investigation of horizontal saccadic eye movements in DRS with high resolution eye movement recording for accurate measurements and precise quantification of the metrics and kinematics of saccades has been useful for improving the understanding of the binocular control of saccades (Yüksel et al., 2005). In this study, the two eyes were recorded simultaneously in binocular viewing condition. Saccade properties were quantitatively analyzed separately in four different categories: centrifugal and centripetal saccades for each side of gaze (affected side and sound side). This approach made possible the interpretation of the underlying innervations and the agonist–antagonist muscle relationship in order to attempt modeling of saccades in DRS type I. Particularly in DRS, the initial position of the two eyes is different depending on the category of eye movement (for instance, when saccades to the sound side are considered, the initial position of the two eyes is different for centripetal movements whereas it is the same for centrifugal movements). In view of the description of the many various types of DRS, it appeared to be very important to study patients with very similar clinical pattern because it emphasized the underlying innervational anomaly. Unilateral DRS type I was interesting because it allowed comparing the affected eye behavior with the sound eye. Saccades of the sound eye were orthometric and accurate with no drift in centripetal and centrifugal direction. This normal behavior was an evidence of the integrity of the interneurons in the abducens nucleus. In view of these results, DRS needs to be considered as a maldevelopment of the abducens motoneurons and not of the abducens nucleus. These findings illustrated a mismatch between the pulse and step of innervation. The relationship between saccade amplitude of the affected eye and the sound eye was linear for all categories of eye movements implying a close coupling between the two eyes. Results brought evidence for conjugate adaptation of the pulse signal of innervation which seemed

to be yoked for the two eyes even though DRS offers clear advantage for independent control. In contrast, separate adaptation of the step signal of innervation was possible for the two eyes.

Binocular recordings permitted the simultaneous observation of the two eyes which present in DRS very different ranges of ocular rotations. The comparison between binocular viewing and monocular viewing (sound eye viewing or affected eye viewing) experiments was essential for gathering information about the adaptation of the brain. The binocular coordination of saccades is essential for achieving binocular vision after every change in fixation. In addition, binocular vision is necessary to ensure binocular oculomotor coordination between the two eyes via adaptive mechanisms. Contrary to comitant strabismus, unilateral DRS type I is peculiar because binocular vision is preserved in one half of the visual field, while there is congenital severe eye misalignment in the other half of the visual field. The coupling of horizontal saccades of the two eyes and their dynamic behavior under binocular and monocular viewing conditions in patients with unilateral DRS type I was reported (Yüksel et al., 2008). Typical traces of centripetal eye movements toward the affected-side gaze, recorded with the search coil technique, for two subjects and in different viewing conditions (binocular viewing: BV, sound eye viewing: SEV, affected eyeviewing: AEV) are illustrated in Fig 6. The comparison between binocular viewing and monocular viewing conditions brought more evidence for validation of the hypothesis that the rapid part of the saccadic command is common for the two eyes. First, affected eye viewing conditions experiments assessed if there was some possibility for increasing the innervation (pulse signal of innervation) of the affected eye in affected-side gaze searching for the existence of some residual innervation of the deficient abducens nerve. Moreover, analysis of the results demonstrated that there was transfer of the adaptation of the affected eye (increase of pulse signal) toward the sound eye (occluded). The relationship between the saccadic amplitude in the AEV condition and the saccadic amplitude in the BV condition for each subject and for each eye is illustrated in Fig 7. Finally, depending on the type of adaptation (the pulse and/or the step component of saccadic command) and the presence of the transfer to the other eye, we shed light on saccadic adaptation mechanisms in a theoretical framework. For saccades, the innervation results from a combination of the pulse and the step signal. In conclusion, monocular adaptation was shown to be possible only for the step of innervation (i.e. controlling the final eye position: monocular adaptation of the step, see gain K in Fig 8) but not for the pulse of innervation (i.e. control-

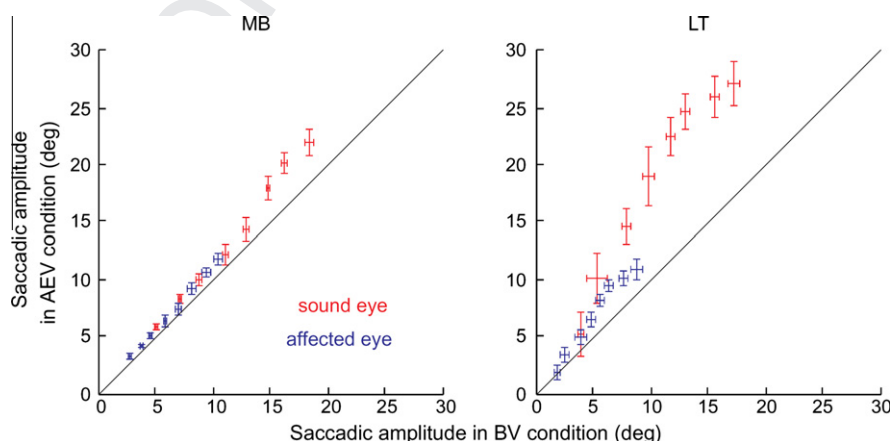


Fig. 7. The diagram represents the relationship between the saccadic amplitude in the AEV condition and the saccadic amplitude in the BV condition for each subject and for each eye (left, subject MB; right, subject LT). Means of saccadic amplitudes for each eye in AEV vs. BV conditions and for each subject were calculated for two degree bins of target step amplitude. For each bin of step amplitude, bi-directional 95% confidence intervals were drawn for each eye (affected eye in blue and sound eye in red) in BV and AEV conditions. Adapted from Yüksel et al. (2005).

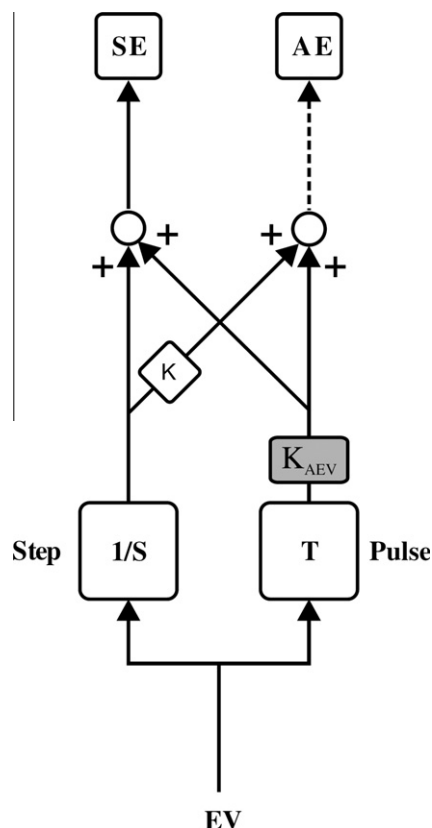


Fig. 8. The innervation results from an association between the pulse and the step signal. The distribution of the innervation signals to the two eyes is represented by this diagram. A signal of pulse and step is directed towards each eye. The motor input from the abducens motoneurons toward the affected eye is drawn as a dotted line. The step to the affected eye is adapted through gain K . The hypothesis for the level of adaptation through gain K_{AEV} (drawn in grey) is illustrated in the diagram. There is possibility of adaptation for the pulse (gain = K_{AEV}) signal coupled for the two eyes and the ability to adapt the step signal separately for each eye (gain K). Adapted from Yüksel et al. (2005).

ling the saccadic gain: yoked adaptation for the pulse, see gain K_{AEV} in Fig 8), even though the peculiarity of DRS type I offered clear advantage for separate pathways of control for the two eyes. The distribution of the innervations signal to the two eyes is represented by the diagram of Fig 8. The most commonly accepted hypothesis of conjugate horizontal eye movements guided by Hering's law of equal innervations for extra ocular muscles seems to be confirmed in DRS even though recent studies have found evidence that some premotor neurons that should encode binocular commands may actually encode monocular commands (King & Zhou, 2000; Zhou & King, 1998). Besides, some clinical observations describe abnormalities producing disjunctive eye movements within the framework of independent control of the two eyes (Dell'Osso, 1994). These results are in agreement with the observations reported in repair properties in peripheral and central 6th nerve palsies (Wong, McReelis, & Sharpe, 2006). Evidence has been given that monocular unidirectional change in saccade speed (pulse signal of innervation) was possible in peripheral palsies but not in central palsies. Explanation was proposed either by regeneration of axons/myelin peripherally or by mechanisms of monocular adaptation. As DRS is a congenital deficit in abducens motoneurons at brainstem level, it seems probable that such mechanisms of monocular adaptation of the pulse signal of innervation are damaged. However, DRS offers compensation by separate adaptation of the step signal of innervation for the two eyes (Fig 8).

10. The interest for modeling saccades in DRS

The goal of theoretical studies on eye movements is to develop models that realistically represent neurobiological processes. Although each aspect of a movement can be explained by many models, the requirement that a single model accounts for as much normal and abnormal behavior as possible constrains the choice of models and reveals isomorphisms that contribute to our understanding of brain function. Thus, a key factor in modeling the neural control of saccades is the interaction between clinical and basic science.

Biomechanical modeling of saccades in DRS type I can have both clinical utility and scientific validity. As a scientific hypothesis, such a model would propose an explanation for the pathogenesis of the oculomotor disorder. Indeed, all available histological, electromyographic and imagery data of DRS brought explanation to the pathogenesis of DRS as being a hypoplasia of motoneurons of the abducens nucleus and nerve on the affected side with secondary anomalous innervation of the affected lateral rectus muscle at a peripheral level by the branches of the oculomotor nerve. But, if we look from bottom-up, there is still uncertainty about the organization of the oculomotor control at the brainstem level. Studying eye movements is an elegant non-invasive way to collect experimental data on DRS. Binocular recordings give information on the conjugacy of saccades. Moreover, monocular viewing condition in binocular recordings gives insight to adaptation of the brain. The parameterization of the properties of saccades is adapted to the pathological condition according to the knowledge of the properties of the studied condition. This allows implementing a mathematical model. This model needs to take into account the abnormal innervation of the affected eye but also the changes in extra ocular muscles properties associated with the condition. The parameters of the model can be tuned on a subject-by-subject basis in order to gain insights into the affected eye plant and its residual innervation for each subject individually. All in all, the model can result in a realistic and idiosyncratic representation of the neurophysiologic process involved in DRS. As a clinical tool, the model will help to assimilate the underlying pathogenic cause to the disorder with direct implication on therapeutical management. Indeed, additional quantitative information on the innervational anomaly of the affected lateral rectus muscle in DRS would be essential to guide surgical management. Electromyography has pitfalls and remains invasive for patient care. Imagery is not precise enough to quantify the anomalous peripheral innervation. Studying saccades and modeling DRS is a promising way to guide clinicians in patient care management (Orban de Xivry, Yüksel, & Lefèvre, 2007).

11. New classification of DRS

Daily practice of medicine requires knowledge of all the clinical symptoms and signs characteristic of a pathology in order to match information with the complaints of the patient. This leads to exact diagnosis, sometimes after performing paraclinical tests to confirm clinical impression. Finally, diagnosis is followed by proposal of appropriate treatment. This difficult task is made somewhat easier with classification of pathological processes. Classification is usually made based on clinical presentation.

General classification of DRS into types I–III was mainly based on clinical features taking into account only the degree of asymmetry between the limitation of adduction and abduction (Von Noorden, 2002). DRS type I was characterized by marked limitation or absence of abduction; normal or only slightly defective adduction; narrowing of the palpebral fissure and retraction on adduction; widening of the palpebral fissure on attempted abduction. DRS

type II was described with limitation or absence of *adduction* with exotropia of the affected eye; normal or slightly limited *abduction*; narrowing of the palpebral fissure and retraction of the globe on attempted adduction. DRS type III was a combination of limitation of both *abduction* and *adduction*; retraction of the globe and narrowing of the palpebral fissure on attempted adduction. Although this terminology has been useful for many years, a particular attention should be given to the complaints of the patient and to careful examination of the head posture, the facial asymmetry, the eye motility and the palpebral fissures on a dynamical basis (through different positions of the head and the gaze). This leads to make a major difference between the subgroups of DRS type I regarding to the abnormal head posture and the misalignment of the eyes in the primary position. Moreover, in view of all the available electromyographic, imaging and eye movement recordings, a new classification of DRS may be more relevant because it will allow linking the clinical description with the degree of innervation anomaly and emphasize the continuum that exists between the different forms of DRS (Souza-Dias, 2009).

Fig. 9A summarizes 6th nerve palsy and different subtypes of DRS type I. The common clinical feature between complete abducens nerve palsy and DRS type I is mainly the limitation of abduction which is present in various degrees regarding the amount of hypoplasia of the involved abducens nerve in parallel with none to some supply from the oculomotor nerve. The classification from left to right is organized in a degressive manner; marked limitation of abduction to almost normal abduction. The amount of fibers that abandon the medial rectus nerve for supply to the lateral rectus is variable; if they are scarce, the medial rectus is much stronger than the lateral rectus and, consequently, the adduction is not significant.



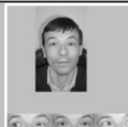

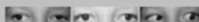


A	Classification	<u>Complete sixth nerve palsy</u>	DRS type I A → <u>Eso-DRS type I</u>	DRS type I C → <u>Ortho-DRS type I</u>	DRS type I B → <u>Exo-DRS type I</u>
	Motility examination				
	Clinical description	<ol style="list-style-type: none"> 1. Complete limitation of abduction (affected eye doesn't reach the midline) 2. Large angle esotropia in primary position 3. Face turn toward the affected side 4. No palpebral retraction in adduction 	<ol style="list-style-type: none"> 1. Complete limitation of abduction (affected eye reaches hardly the midline) and near to normal adduction 2. Small angle esotropia in primary position 3. Face turn toward the affected side 4. Mild palpebral retraction in adduction 	<ol style="list-style-type: none"> 1. Marked limitation of abduction (affected eye crosses slightly the midline) and slightly defective adduction 2. No ocular deviation in primary position 3. No torticollis 4. Marked narrowing of the palpebral fissure in adduction 	<ol style="list-style-type: none"> 1. Mild limitation of abduction and mild limitation of adduction 2. Small angle exotropia in primary position 3. Face turn toward the sound side 4. Marked narrowing of the palpebral fissure in adduction
B	Classification	DRS type III → <u>DRS type II</u>	DRS type II → <u>DRS type III</u>	Synergistic divergence = <u>Variant of DRS type II with simultaneous abduction</u>	
	Motility examination				
	Clinical description	<ol style="list-style-type: none"> 1. Mild to marked limitation of abduction and marked limitation of adduction 2. Small angle exotropia in primary position 3. Face turn toward the sound side 4. Marked narrowing of the palpebral fissure in adduction 	<ol style="list-style-type: none"> 1. Near to normal abduction and complete limitation of adduction 2. Exotropia in primary position 3. Face turn toward the sound side 4. Marked palpebral retraction in adduction 	<ol style="list-style-type: none"> 1. No adduction, near to normal abduction, excessive abduction when attempt to adduction 2. Large angle exotropia in primary position 3. Face turn toward the sound side 4. No narrowing of the palpebral fissure on attempted adduction 	

Fig. 9. New classification of various subtypes of DRS according to the underlying innervational deficit. (A) Comparison between complete 6th nerve palsy and subgroups of DRS type I. (B) Update of classification of DRS types II and III.

cantly impaired; the bridle effect produced by the co-contraction is minor, with consequent small retraction in adduction and no anomalous vertical deviations (up and downshoot). If the number of fibers that abandon the medial rectus nerve toward the lateral rectus is greater, there is lesser difference in forces between the medial and the lateral recti in adduction, because the innervation of the medial rectus is reduced and the one of the lateral rectus is increased. The adduction starts to be somewhat impaired, the bridle effect is stronger, with larger retraction, and there can be small anomalous vertical movements. This phenomenon leads to progressive change in the compensatory abnormal head posture; turn toward the affected side, no torticollis, turn toward the sound side. Complete abducens nerve palsy (Fig. 9A, first column) represents complete absence of residual innervation (=0) and no supply from the oculomotor nerve (=0). Eso-DRS type I (Fig. 9A, second column) is explained by some residual innervation of the abducens nerve and some supply from the oculomotor nerve in a ratio of 3rd nerve supply < 6th nerve residual innervation. Ortho-DRS type I (Fig. 9A, third column) represents a ratio of 6th nerve supply = 6th nerve residual innervation. Exo-DRS type I (Fig. 9A, fourth column) represents a ratio of 3rd nerve supply > 6th nerve residual innervation.

Fig. 9B compares DRS types II, III and synergistic divergence. DRS types I and III are in fact a continuum as the number of fibers that abandon the medial rectus nerve increases, which leads this muscle to lose force and the lateral rectus to gain force in its abnormal contraction, until arriving to the situation in which their forces equalize themselves (symmetric co-contraction). In this situation there is no adduction or abduction (the abducens nerve is absent), the bridle effect of the co-contraction is maximal and consequently the retraction and the anomalous vertical movements are more evident. Therefore, it is more relevant to **re-name type III as type II**. The increase of the amount of residual innervation of the abducens nerve leads to **DRS type II that should be renamed type III** because the abduction becomes near to normal (Fig. 9B, second column). The clinical motility deficit is inversed with marked limitation of adduction greater than the limitation of abduction. Moreover, this form of DRS must be particularly distinguished because the presence of abducens nerve has been shown to be preserved on MRI studies in some forms of DRS (Kim & Hwang, 2005b). The final type is a variant of DRS type II with simultaneous abduction, in fact an extreme form (Fig. 9B, third column). If the number of fibers that leave the medial rectus nerve toward the lateral rectus is still greater, one arrives to the situation classically known as **synergistic divergence**. The clinical pattern is fantastic. The lateral rectus becomes stronger than the medial rectus in the co-contraction and, consequently, in the attempt of adduction the affected eye abducts instead of adducting. When the sound eye abducts, the affected one also abducts obeying the Sherrington equal innervation law. It seems to be mainly a misdirection syndrome more than a basic maldevelopment of the oculomotor neurons. The basic etiology for this rare oculomotor disorder is still unknown.

The purpose of this new classification mainly aims at understanding the underlying innervational abnormalities with correlation to the observed clinical pattern and to reflect the continuum between the different types of DRS. The quantification of the amount of residual innervation of the abducens nerve and the amount of supply from the oculomotor nerve can be obtained by modeling saccades. In spite of all these considerations, these two tables give a guideline for approaching the different subtypes of DRS which are often confused. Careful attention to the description of the type of DRS is essential to interpret results of imaging or eye movement recordings studies and is certainly very useful for guiding the clinician in the management of the patient.

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